이학박사학위논문

강박증 환자군의 부정 정서 하에 배외측 전전두엽에서 안와전두엽으로의 경로 이상

Disruption of effective connectivity from the dorsolateral prefrontal cortex to the orbitofrontal cortex by negative emotional distraction in obsessive-compulsive disorder

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Disruption of effective connectivity from the dorsolateral prefrontal cortex to the orbitofrontal cortex by negative emotional distraction in obsessive-compulsive disorder

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To the Faculty of the

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Abstract

Disruption of effective connectivity from the dorsolateral prefrontal cortex to the orbitofrontal cortex by negative emotional distraction in obsessive-compulsive disorder

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Background. Obsessive-compulsive disorder (OCD) has been associated with abnormal cognitive and emotional functions and these dysfunctions may be dependent on the disruption of dynamic interactions within neuronal circuits associated with emotion regulation. Although several studies have shown the aberrant cognitive-affective processing in OCD patients, little is known about how to characterize effective connectivity of the disrupted neural interactions. In the present study, we applied effective connectivity analysis using dynamic causal modeling (DCM) to

explore the disturbed neural interactions in OCD patients.

Method. Twenty patients and 21 matched healthy controls performed a delayed-response working memory (WM) task under emotional or non-emotional distraction while undergoing functional magnetic resonance imaging (fMRI).

Results. During the delay interval under negative emotional distraction, both groups showed similar patterns of activations in the amygdala. However, under negative emotional distraction, the DLPFC and the OFC exhibited significant differences between groups. Bayesian model averaging indicated that the connection from the DLPFC to the OFC was negatively modulated by negative emotional distraction in patients, when compared to healthy controls ($p < 0.05$, Bonferroni-corrected).

Conclusions. Exaggerated recruitment of the DLPFC may induce the reduction of top-down prefrontal control input over the OFC, leading to abnormal cortico-cortical interaction. This disrupted cortico-cortical interaction under negative emotional distraction may be responsible for dysfunctions of cognitive and emotional processing in OCD patients and may be a component of the pathophysiology associated with OCD.

Keywords: Dorsolateral prefrontal cortex, emotion, fMRI, obsessive-compulsive disorder, orbitofrontal cortex.

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Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent and intrusive thoughts (obsessions) accompanied by anxiety and repetitive behaviors (compulsions) to relieve the obsessional distress. Patients with OCD report inability to regulate such disturbing thoughts and feelings with anxiety, leading to compulsive behaviors (Milad and Rauch, 2012). Although OCD patients are aware of the irrationality of compulsive habits, overwhelming anxiety prevents the patients from resisting the repetitive (compulsive) acts (Taylor and Liberzon, 2007). In this case, inexorable thoughts combined with the feelings of anxiety can be associated with an abnormal interaction between cognition and emotion. This abnormal cognitive-affective interaction is further manifested in OCD patients by inflexible adoption of efficient learning strategies in an OCD-specific context (Zetsche *et al.*, 2014). On a neurobiological level, the cognitive-affective dysfunction in OCD patients may relate to the unsuccessful neural interactions within brain circuits associated with emotion regulation.

The interplay between the amygdala and the prefrontal cortex such as the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (dmPFC), ventromedial prefrontal cortex (vmPFC), and orbitofrontal cortex (OFC) is involved in emotion regulation including cognitive control, inhibitory control or voluntary down-regulating of emotion, especially negative emotion

(Ochsner *et al.*, 2004, Ochsner and Gross, 2005, Phillips *et al.*, 2008). The amygdala is assumed to mediate identification of potential threat and evaluation of affective values (Davis, 1992, Davis and Whalen, 2001). In OCD patients, previous studies have observed abnormal responsiveness in the amygdala to negative emotional stimuli or symptom-provoking stimuli (Cannistraro *et al.*, 2004, Lawrence *et al.*, 2007, Simon *et al.*, 2010, Cardoner *et al.*, 2011, de Wit *et al.*, 2015). However, the exaggerated amygdala activation during OCD symptom provocation was dampened by attentional distraction (Simon *et al.*, 2014). Besides the amygdala, the DLPFC is associated with cognitive control to maintain of task-related requirements in the presence of task-irrelevant negative emotional distraction (Dolcos and McCarthy, 2006, Dolcos *et al.*, 2011) and effortful processing that accompanies reappraisal (Phillips *et al.*, 2008). In studies with OCD patient, increased prefrontal engagements including the DLPFC were observed during symptom provoking picture presentations, reflecting the prefrontal hyperactivation as the top-down cognitive control over affective responses in the amygdala (Simon *et al.*, 2013, Simon *et al.*, 2010). In a working memory task with no emotional stimuli, however, OCD patients exhibited no significantly different task-related DLPFC activation relative to healthy controls (van der Wee *et al.*, 2003). Within the fronto-limbic interplay, patients with OCD showed enhanced working memory task-related prefrontal demands and increased functional coupling between the prefrontal regions including the DLPFC and amygdala (de Vries *et al.*, 2014). However, a recent functional

connectivity study revealed that OCD patients exhibited less DLPFC engagement and dmPFC-amygdala connectivity during down-regulation of negative affect (de Wit *et al.*, 2015).

Moreover, the interplay between the DLPFC and OFC is critical in cognitive-affective interaction and its disruption can be a component of the pathophysiology in psychiatric disorders (Moghaddam and Homayoun, 2008). In conjunction with the DLPFC, the OFC has an important role for effective inhibitory control in a delayed working memory (WM) task (Petrides, 2000). Also, the OFC plays an integral role, acting as a hub to integrate and modulate brain activation in order to regulate the cognitive-affective responses (Rule *et al.*, 2002, Evans *et al.*, 2004). Anatomically the OFC has extensive and reciprocal connections with the DLPFC and amygdala so that it may help mediate the interaction between the DLPFC and amygdala during emotion regulation (Phillips *et al.*, 2008). As a cytoarchitecturally or functionally heterogeneous region, the OFC is characterized by its subregions. The anterior part of the OFC is interconnected to the DLPFC and is involved in cognitive processing, whereas the posterior part is interconnected to the amygdala and is associated with emotional functions (Zald and Kim, 1996, Choi *et al.*, 2004, Kwon *et al.*, 2009). A previous study showed that the OFC was engaged in cognitive reappraisal of negative emotion, whereas the DLPFC was more generally recruited for cognitive control regardless of emotion types in emotion regulation (Golkar *et al.*, 2012).

Despite a number of studies on abnormal neural responses underlying

cognitive and emotional processing in OCD patients, it remains unclear how to define the effective connectivity and causal relationship of the aberrant neural interplay within the single components of emotion regulation circuits. In the current study, dynamic causal modeling (DCM) was employed to examine and model the effective connectivity on fMRI data of OCD patients and healthy controls during a delayed WM task under negative emotional distraction. In univariate findings, we hypothesized that OCD patients would exhibit dysfunctions within emotion regulation circuits. More precisely, we expected that the task irrelevant negative emotional distraction during a WM task causes hyperactivations in the prefrontal regions, especially in the DLPFC for cognitive control and the amygdala activation for emotional processing in patient with OCD. Concerning the DCM analysis, we hypothesized that consistent with an altered cognitive control exerted by the DLPFC, exaggerated DLPFC engagement in patient with OCD is related to altered connectivity between the DLPFC and the amygdala or other frontal regions underlying emotion regulation. In particular, we predicted that OCD patients would have the abnormal modulation effect by negative emotional distraction on effective connectivity between the DLPFC and OFC, as these regions are critical for cognitive control to inhibit emotional responses.

Material and Method

Participants

A total of 24 OCD patients were recruited from the OCD clinic at Seoul National University Hospital. The diagnosis and comorbidity were established by board-certified psychiatrists with Structured Clinical Interview for DSM-IV Axis-I and II disorders (SCID-I and II). Also 23 control subjects were recruited and matched for sex, age, IQ and handedness through an internet advertisement. All healthy controls were pre-screened by the Structured Clinical Interview for *DSM-IV* Axis I Disorders Non-Patient Edition (First *et al.*, 1996). Exclusion criteria for all participants included a history of psychosis, bipolar disorder, Tourette's disorder or other tic-related conditions, traumatic brain injury, epilepsy, alcohol or substance abuse, intellectual disability (IQ < 70), and any other neurological diseases. Four OCD patients and 2 control subjects were excluded from the final analysis due to excessive head movements. Among the remaining 20 OCD patients, 15 OCD patients were not been diagnosed with any comorbid Axis I and II disorders, and 5 had the following disorders: major depressive disorder (N = 3), parasomnia NOS (N = 1), obsessive compulsive personality disorder (N =1), and schizoid personality disorder (N =1). There were 5 non-medicated (drug-free for at least 4 weeks) OCD (UMO) patients and 4 drug naïve OCD (DNO) patients at the time of study. Eleven OCD patients were medicated with a stable dosage at least 4 weeks before scanning. They were taking at least one selective serotonin

reuptake inhibitor (SSRI) (fluoxetine, N = 7; escitalopram, N = 2; sertraline, N = 1; Paroxetine, N = 1), dopamine and noradrenaline reuptake inhibitor (bupropion, N = 1), and anxiolytics or sedatives (clonazepam, N = 5; zolpidem, N = 1). Among them, 3 patients received low dose atypical antipsychotics for adjuvant treatment (risperidone, N = 1; aripiprazole, N = 2).

Experienced psychiatrists performed the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman *et al.*, 1989a, Goodman *et al.*, 1989b) to assess the severity of the OCD symptoms in each OCD patient. All patients completed a measure of depression and anxiety levels using Beck Depression Inventory (BDI) (Beck *et al.*, 1961) and Beck Anxiety Inventory (BAI) (Beck *et al.*, 1988), respectively. We classified the OCD patients according to the five clinical dimensions (Mataix-Cols *et al.*, 1999) and excluded patients with hoarding symptoms due to their different neural involvement from non-hoarding OCD patients (Lochner *et al.*, 2005, Saxena *et al.*, 2004). Predominant obsession/compulsions were as follows: contamination/cleaning (N = 9), aggressive/checking (N = 3), miscellaneous (N = 6), and symmetry/ordering (N = 2).

All participants had normal or corrected-to-normal vision. This study was approved by the Seoul National University Hospital institutional review board (H-1112-050-389) and the protocols were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and from the parents of those who were under 18 years old.

Procedure

The study design modified the previous design from Dolcos and McCarthy (Figure 1.; Dolcos and McCarthy, 2006). All subjects performed a modified delayed WM task with distracters presented during the delay interval. Three similar faces (female faces for 50% of trials) were presented as the memoranda. The faces were selected from databases of Korea Facial Expressions of Emotion (KOFEE; Park et al., 2011) and the Korea University Facial Expression Collection (KUFEC; Lee et al., 2006). The visual distracters consisted of negative emotional scenes, neutral scenes, and digitally scrambled pictures. The negative emotional and neutral pictures were selected from the International Affective Pictures System (IAPS) (Lang *et al.*, 1997). A pool of 108 trials was divided into 6 runs, which consisted of 18 trials each (6 negative emotional, 6 neutral and 6 scrambled). The trials in each run were presented in a pseudorandomized order, and no more than two consecutive trials of the same type were presented. Each trial began with the presentation of 3 similar faces of memoranda for 3 s, which subjects were required to encode and then maintain them into WM during the delay interval between the offset of the memoranda and the onset of the memory probe (7 s). After a delay of 1 s, 2 pictures of the same distracter type were consecutively presented for 5 s (2.5 s each), and subjects were instructed to look at these distracters while maintaining focus on the previously presented memoranda. Another a delay of 1 s was presented before the probe. A single face as a probe

was presented for 1.5 s, and participants were asked to respond whether the single face was one of the 3 faces in the memoranda or a new face (old faces for 50% of the trials) as quickly and accurately as possible while the probe was on the screen. In order to allow the hemodynamic response to return to the baseline, a fixation was presented for 10.5 s.

After fMRI scanning, healthy controls and OCD patients performed 2 and 3 consecutive rating tasks, respectively. All subjects were required to record subjective reports on the meaningful pictures for intensity and distractibility (as perceived during the WM task). The OCD patients had one more rating task for symptom provocation. All rating tasks used a 4-point Likert scale (1, lowest; 4, highest; 0, none for symptom provocation). These subjective reports were averaged for all the participants and further used as covariates to investigate the link between behavioral responses and brain activity.

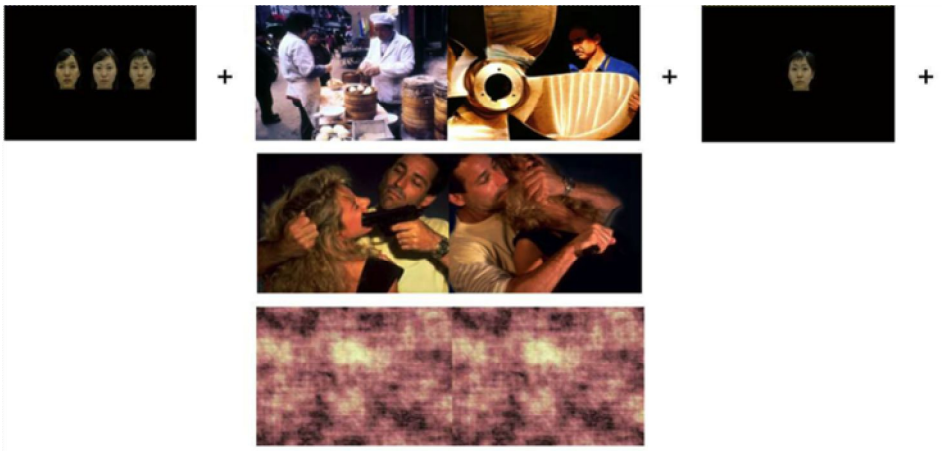

Figure 1. Diagram of the delayed working memory task. Subjects were instructed to encode the memoranda (3 faces) and maintain them into working memory while looking at distracters. Lastly, subjects were asked to respond whether the single face (as a probe) was one of the 3 faces in the memoranda or a new face. Three types of distracters (negative emotional, neutral, and scrambled) were presented during the working memory delay period. Each trial contained two distracters of the same type. The study design modified the previous design from Dolcos and McCarthy (Dolcos and McCarthy, 2006).

Image acquisition

Blood oxygenation level dependent (BOLD) contrast functional images were acquired with echo-planar T2*-weighted (EPI) imaging using a 3-T scanner (Siemens Magnetom Trio, Erlangen, Germany). Each image volume consisted of a series of 27 functional slices with a 1 mm inter-slice gap (axial plane; repetition time = 2 s; echo time = 30 ms, flip angle = 90°, field of view = 220 mm, voxel size = 3.4 x 3.4 x 4

mm^3). Three-dimensional T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) images were acquired in 208 slices (repetition time = 1.67 s; echo time = 1.89 ms, flip angle = 9°, field of view = 250 mm, voxel size = 0.9 x 0.9 x 1 mm^3).

Behavior data analysis

Demographic and clinical data were compared across groups using independent sample *t*-tests and chi-square tests. Behavioral data were analyzed with the 3 different distracter types (negative emotional vs. neutral vs. scrambled) as the within-subject variable and groups (healthy controls vs. OCD) as the between-subject variable using repeated measures ANCOVAs with BDI scores, age and sex as covariates. If data did not meet parametric assumptions, nonparametric tests were used.

fMRI preprocessing and analysis

Functional imaging analysis was conducted by the following preprocessing steps using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) after discarding the first 3 volumes of each session: slice timing, motion correction, coregistration, normalization (3 mm^3 resampling voxel size), and smoothing (8 mm^3 kernel). A total of 206 volumes were acquired in each session. For the first-level analysis, 5 experimental conditions were included in each run: memoranda, the 3 types of distracters during the delay interval (negative emotional, neutral, scrambled), and

probe, as well as 6 motion regressors for each session. Contrast images obtained from the first-level analysis were entered into the second-level 3 x 2 full factorial model with the distracter types (negative emotional, neutral, scrambled) and factors group (healthy controls, OCD) including BDI scores, age and sex as covariates. This factorial design included the 'main effect of distracter types' as the within group comparisons, the 'main effect of groups' as the between group comparisons, and the 'interaction effect of distracter types x groups'. Our contrast of interest was the effect of negative emotional distraction on ongoing WM task (negative emotional > scrambled). We predefined the following regions of interest (ROIs): DLPFC (Brodmann area (BA) 9 and 46), OFC (BA 11 and 12), VLPFC (BA 47), dmPFC (BA 9 and 10), and vmPFC (BA 11) and amygdala using a predefined anatomical mask or the automatic anatomic labels implemented in the WFU PickAtlas (Wake Forest University School of Medicine, Winston-Salem, North Carolina; http://www.fmri.wfubmc.edu/cms/software). We determined a significant threshold level of $p < 0.05$, whole brain family-wise error (FWE) corrected for multiple comparisons, as well as Bonferroni-corrected for the number of ROIs (Small Volume Correction, SVC; $p_{\text{FWE-SVC}} < 0.008$ as significant; $0.008 < p_{\text{FWE-SVC}} < 0.05$ as trend significant; Worsley et al., 1996). To specifically assess the pattern of activity, we used the MarsBar tool box (http://marsbar.sourceforge.net) to extract percent signal change data from peak coordinates of ROIs with a 6 mm radius sphere. Additional correlation analyses between the extracted percent signal change data and behavioral data were performed using PASW

Statistics 18 (SPSS). For nonparametric variables, Spearman's rho was used. All analyses included only correct trials.

Dynamic causal modeling

To investigate if there were group differences on effective connectivity in the neural circuits associated with emotion regulation, DCM 10 as implemented in SPM8 was used. In DCM, a Bayesian model comparison procedure was used to estimate hidden neuronal effective (causal) connectivity and its modulation effect by experimental manipulations. DCM allows modeling of the task-independent intrinsic connectivity (DCM.A), of the task-dependent modulatory effect (DCM.B) by experimental manipulation on the endogenous coupling, and of the direct influence on individual or groups of regions (DCM.C).

Time series extraction

The ROIs with between-group differences (right DLPFC, x/y/z = 39/44/37; OFC, x/y/z = 27/50/-14) were chosen as seeds (see Results). The right amygdala (x/y/z = 27/-1/-26) as negative emotional effects and the right visual cortex (V1, x/y/z = 45/-79/-8) as a direct driving input were derived from the whole-brain main effect of the distracter types across all subjects. All regions were right-lateralized, where the strongest group activations were found. The observed lateralization is also in accordance with previous findings, which detected a greater

impact on the right prefrontal regions by negative emotional distracters during the delay period (Dolcos *et al.*, 2008, Dolcos and McCarthy, 2006). Additionally, previous studies suggested a functional specialization of the right amygdala for the processing and encoding of nonverbal affective stimuli (Anderson *et al.*, 2003, Ochsner *et al.*, 2004). Each subject's activation maxima within a sphere of 6-mm at a single-subject significance threshold $p < 0.1$ was used to center and then extracted the first eigenvariate. One subject from each group was excluded for no significant activations in the 3 regions.

Model space

In a previous study (Sladky *et al.*, 2013), Bayesian model averaging (BMA) was used, which provides averages of parameter estimates within the entire model space weighted by the posterior probability for each model (Hoeting *et al.*, 1999, Penny *et al.*, 2010). The inference on model structure can be one method to compare the winning models of the OCD patients and healthy controls, however, the method can be insufficient due to a possibility that the OCD-related deficits are mediated by abnormal modulation effects rather than disruption on model structure (Sladky *et al.*, 2013). Therefore, BMA is an alternative approach for comparing parameter estimates across groups, and therefore can explain the uncertainty regarding model structure (Stephan *et al.*, 2010).

We created DCM models as an initial model space to select

connections among the right DLPFC, OFC, and amygdala with significant posterior evidence and to remove improper connections for the sake of computational complexity. Based on the previous neurobiological evidence (Kringelbach and Rolls, 2004, Diwadkar *et al*., 2012), we set bidirectional connections between the amygdala and the OFC and from the amygdala to the DLPFC. Then, DCM models were generated with possible anatomical connectivity configurations between the DLPFC and the OFC, and from the DLPFC to the amygdala, yielding an initial model space of 8 models. A direct visual input entered the V1 as a driving input, which has a unidirectional connection both to the DLPFC and the amygdala in all DCM models (Ongur and Price, 2000).

Based on the chosen connectivity from the initial model space in each group, connections that were not significant in both groups were removed in further DCM analysis. All other significant connections were used as a revised model space. In this revised model space, modulation effects by negative emotional distraction were additionally introduced. According to possible modulatory effects by negative emotional distraction on each connection, a total of 25 model configurations were created (Figure 2). BMA averaged the connectivity parameter estimates and their modulations within each subject's 25 models, and these results were analyzed using one-sample and two-sample t tests at a threshold of $p < 0.05$, both Bonferroni-corrected for multiple comparisons and uncorrected. For nonparametric data, nonparametric tests were used.

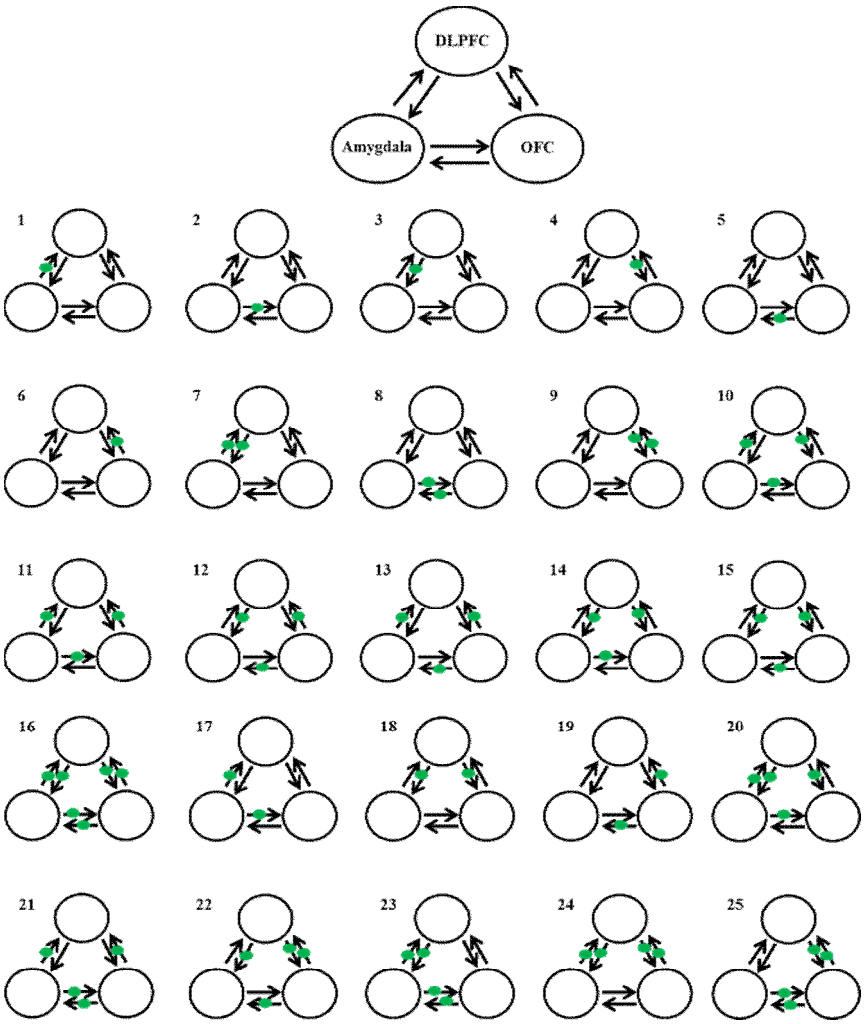

Figure 2. In the revised DCM model space, there were total 25 models according to the patterns of modulatory effects by negative emotional distraction on bidirectional connections among the right dorsolateral prefrontal cortex (DLPFC), amygdala, and orbitofrontal cortex (OFC). Each arrow indicates the intrinsic connectivity, and green dot indicates the modulatory effect.

Results

Demographic and behavioral results

Demographic and clinical data and behavioral results for each group are shown in Table 1 and 2, respectively. Friedmann's ANOVA showed that RTs for each separate group showed no significant differences (OCD patients, $\chi^2 = 2.80$, $p = 0.247$; healthy controls, $\chi^2 = 0.286$, $p = 0.867$). Between-group comparisons did not reveal any significant differences on RTs (Mann-Whitney U test; negative, $p = 0.118$; neutral, $p = 0.112$; scrambled, $p = 0.192$). In the correct rates, there were no significant main effects of distracter type, group and interaction effects ($F = 0.228$, $p = 0.797$; $F = 0.019$, $p = 0.891$; $F = 0.578$, $p = 0.564$, respectively). The average scores for emotional intensity and distractibility did not differ between groups (intensity for negative: controls, 2.56; patients, 2.30, $p = 0.137$; intensity for neutral: controls, 1.43; patients, 1.43, $p = 0.997$; distractibility for negative: controls, 2.20; patients, 1.88, $p = 0.113$; distractibility for neutral: controls, 1.32; patients, 1.45, $p = 0.475$). In OCD patients, the average symptom provocation scores were 1.05 (*S.D*, 1.05) for negative and 0.61 (*S.D*, 0.90) for neutral.

Table 1. Demographic characteristics of the subjects

Variable	OCD patients (N = 20)	Healthy controls (N = 21)	Statistic	*p*-value
Age (years)	25.500 ± 5.405	22.571 ± 4.501	t = -1.889	0.066
Sex (M/F)	12/8	14/7	χ^2 = 0.196	0.658
Handedness (right/left/both)	18/1/1	20/0/1	χ^2 = 1.082	0.582
Education (years)	14.421 ± 1.677	14.143 ± 1.590	t = -0.538	0.593
IQ	107.650 ±13.971	110.476 ±12.628	t = 0.680	0.500
BDI	19.600 ± 10.630	5.476 ± 5.164	t = -5.369	< 0.001
BAI	22.350 ± 11.891	3.905 ± 4.784	t = -6.457	< 0.001
Age of Onset (years)	18.450 ± 5.577			
Duration of illness (years)	7.050 ± 4.861			
Y-BOCS	23.900 ± 7.115 (8-36)			
Y-BOCS obsession	12.600 ± 3.440 (5-18)			
Y-BOCS compulsion	11.800 ± 4.213 (3-18)			
HAM-D	8.850 ± 5.715 (2-23)			
HAM-A	7.450 ± 4.872 (2-20)			

Means and standard deviations (S.D.) for healthy controls and OCD patients (OCD) were given. BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression.

Table 2. Behavioral results

		OCD patients	Healthy controls
RTs (s)	Negative	1.064 ± 0.284	0.949 ± 0.181
	Neutral	1.069 ± 0.272	0.944 ± 0.145
	Scrambled	1.020 ± 0.234	0.936 ± 0.161
CRs (%)	Negative	76.944 ± 11.042	78.439 ± 8.954
	Neutral	71.667 ± 8.949	71.429 ± 10.692
	Scrambled	78.750 ± 9.676	77.116 ± 8.736

Means and standard deviations (S.D.) for healthy controls and OCD patients (OCD) were given. RTs, Response Times; CRs, Correct Rates.

fMRI results

The main effect of the distracter types was found in the bilateral VLPFC (BA 47), amygdala, DLPFC (BA 9/46), lateral parietal cortex (BA 40), inferior temporal cortex (BA 20), OFC (BA 11/12), anterior prefrontal cortex (BA10), occipital cortex (BA 19), dmPFC (BA 9/10), and vmPFC (BA 11) across groups, which included our ROIs (p < 0.05, either whole brain FWE-corrected or FWE-SVC; Figure 3a and Table 3). In the within-group analyses, the healthy controls showed the dmPFC (BA 10), vmPFC (BA 11), VLPFC (BA 47), amygdala, middle temporal cortex (BA 21), occipital cortex (BA 19) while performing a WM task under negative emotion distraction (i.e., negative emotion > scrambled condition; p < 0.05, either whole brain FWE-corrected or FWE-SVC; Table 4). The patient with OCD exhibited the DLPFC (BA 9/46), OFC (BA 11/12), dmPFC (BA 10), vmPFC (BA 11), VLPFC (BA 47), amygdala, superior parietal cortex (BA 5/7), and occipital cortex (BA 19) activations (i.e., negative emotion > scrambled

condition; $p < 0.05$, either whole brain FWE-corrected or FWE-SVC; Table 4). For the main effect of group over all conditions, there were significant differences between groups in the OFC (BA 11/12), DLPFC (BA 9/46), superior temporal cortex (BA 22), and occipital cortex (BA 19) ($p < 0.05$, either whole brain FWE-corrected or FWE-SVC; see Table 3), which included our main ROIs, DLPFC and OFC (DLPFC at $p_{FWE\text{-}SVC} = 0.029$; OFC at $p_{FWE\text{-}SVC} = 0.004$). There was no significant group x task interaction effect. The analysis to test the pattern of activity revealed that OCD patients exhibited the DLPFC (BA 9/46) and OFC (BA 11/12) activations under negative emotional distraction, whereas healthy controls showed deactivations in these regions (Figure 3c and 3d). Plus, a similar pattern of activity was observed in the bilateral amygdala in both groups (Figure 3b).

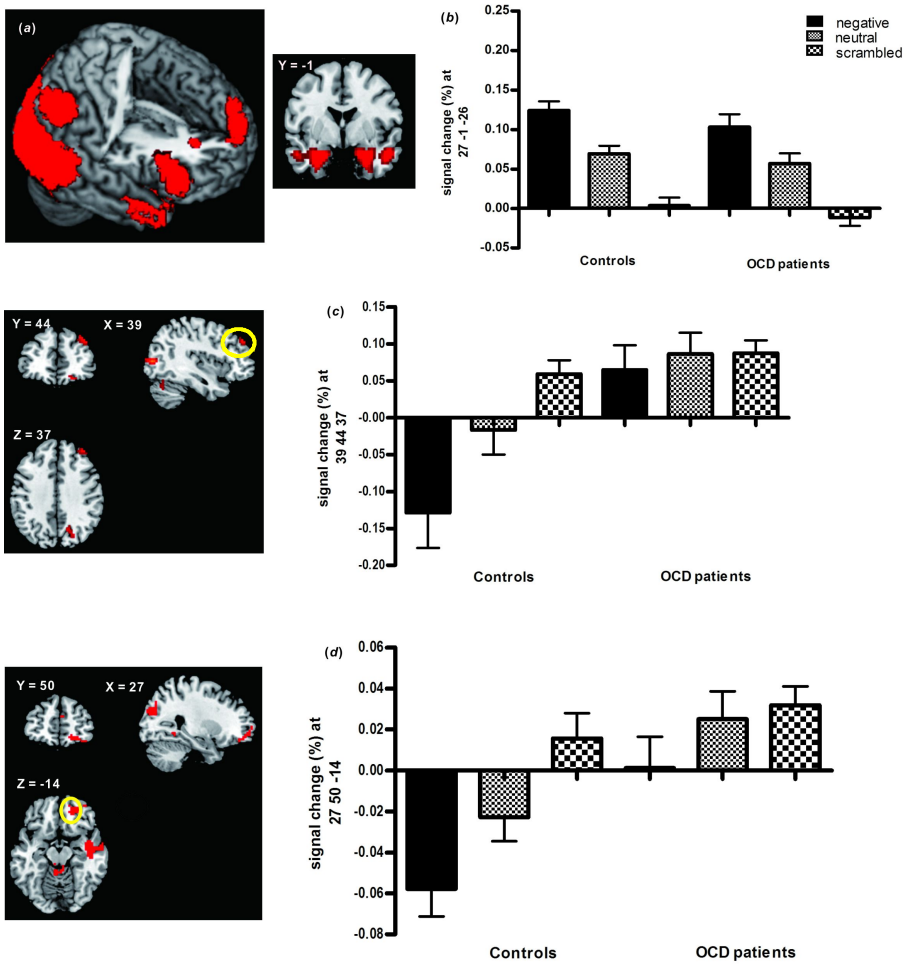

Figure 3. Main effect of task (distracter types) and group. (*a*) Whole-brain analysis of the main effect of distracter types ($p < 0.05$, whole-brain FWE-corrected). (*b*) Pattern of activity in the right amygdala ($p_{FWE\text{-}SVC} < 0.05$). The right amygdala activation was significantly greater in negative emotional distraction in both healthy controls and OCD patients, and there was no significant group difference. The left amygdala had a similar pattern of activity to the right amygdala. (*c*) OCD patients exhibited the increased DLPFC activation (BA 9/46) (at trend level, $0.008 < p_{FWE\text{-}SVC} < 0.05$) in negative emotional distraction, whereas healthy controls showed deactivations in this region. (*d*) The right OFC (BA 11/12) showed a significant group difference under negative emotional distraction ($p_{FWE\text{-}SVC} < 0.05$).

Table 3. Main effect of task (distracter types) and group

Region	H	BA	MNI coordinates (*x, y, z*)	k_e	*Z*	*p*-FWE
Main effect of distracter types						
Amygdala	L		-24, -4, -23	45	Inf.	< 0.001
	R		27, -1, -26	51	Inf.	< 0.001
Orbitofrontal cortex	L	11/12	-24, 44, -8	11	4.48	0.001
	R	11/12	24, 50 -14	7	4.04	0.005
	R	11/12	45, 34, -14	3	5.90	< 0.001
Dorsolateral prefrontal cortex	L	9/46	-57, 26, 16	7	5.54	< 0.001
	R	9/46	48, 17, 25	59	5.93	< 0.001
	R	9/46	39, 35, 37	14	3.89	0.040[b]
Dorsomedial prefrontal cortex		10	0, 62, 25	212	6.82	< 0.001[a]
Ventromedial prefrontal cortex		11/12	0, 53 -20	37	6.71	< 0.001[a]
Ventrolateral prefrontal cortex	L	47	-42, 29, -14	30	7.27	< 0.001
	R	47	54, 35, 4	22	Inf.	< 0.001
Anterior prefrontal cortex	R	10	39, 53, 4	29	5.57	0.001[a]
Middle frontal cortex	L	6	-24, 17, 58	2	4.62	0.042[a]
Lateral parietal cortex	L	40	-48, -55, 46	197	6.54	< 0.001[a]
	R	40	54, -58, 46	228	7.20	< 0.001[a]
Inferior temporal cortex	L	20	-63, -28, -20	2	4.73	0.027[a]
	R	20	60, -25, -26	11	5.78	< 0.001[a]
Occipital cortex	L	19	-45, -82, -8	9495	Inf.	< 0.001[a]
	R	19	45, -79, -8		Inf.	< 0.001[a]

Main effect of group						
Orbitofrontal cortex	R	11/12	27, 50, -14	12	4.06	0.004
Dorsolateral prefrontal cortex	R	9/46	39, 44, 37	10	3.96	0.029[b]
Superior temporal cortex	R	22	45, -22, -5	11	5.03	0.006[a]
Occipital cortex	L	19	-18, -82, 25	85	6.77	< 0.001[a]
	R	19	18, -91, 22	11	5.35	0.001[a]

p-FWE = *p* value with family-wise error correction for the search volume.

BA, Brodmann area; FWE, family-wise error; H, hemisphere; K_e, cluster size; L, left; R, right; *Z*, *Z* score.

[a] Significant at $p < 0.05$, whole-brain family-wise error corrected

[b] Significant at trend-level $0.008 < p_{FWE\text{-}SVC} < 0.05$

Table 4. Effect of task for each separate group

Region	H	BA	MNI coordinates (*x*, *y*, *z*)	k_e	*Z*	*p*-FWE
Healthy controls: *Negative emotional > scrambled*						
Occipital cortex	L	19	-45, -79, -8	5932	Inf.	< 0.001[a]
	R	19	45, -75, -8		Inf.	< 0.001[a]
Middle temporal cortex	R	21	51, 2, -26	157	6.70	< 0.001[a]

Dorsomedial prefrontal cortex	R	9	12, 59, 40	11	5.47	0.001[a]
		10	0, 62, 28	18	5.06	0.005[a]
Ventromedial prefrontal cortex		11	0, 53, -20	7	4.92	0.010[a]
Ventrolateral prefrontal cortex	L	47	-42, 29, -14	18	6.29	< 0.001
	R	47	54, 35, 4	17	7.32	< 0.001
Amygdala	L		-24, -4, -23	40	6.92	< 0.001
	R		27, -1, -26	34	6.20	< 0.001
OCD patients: *Negative emotional > scrambled*						
Occipital cortex	L	19	-45, -79, -8	5613	Inf.	< 0.001[a]
	R	19	48, -79, -5		Inf.	< 0.001[a]
Hippocampus	L		-24, -7, -20	350	5.93	< 0.001[a]
Dorsomedial prefrontal cortex		10	0, 62, 25	123	5.77	< 0.001[a]
Ventromedial prefrontal cortex		11	0, 44, -23	20	5.05	0.005[a]
Superior parietal cortex	L	5/7	-24, -61, 55	13	4.89	0.011[a]
	R	5/7	27, -55, 55	3	4.62	0.035[a]
Inferior frontal cortex	L	45	-57, 26, 16	4	4.78	0.018[a]
Dorsolateral prefrontal cortex	L	9/46	-54, 29, 19	2	4.54	0.003
	R	9/46	48, 20, 25	32	6.30	< 0.001

Orbitofrontal cortex	L	11/12	-36, 35, -14	6	4.23	0.002
	R	11/12	42, 35, -14	2	5.07	< 0.001
Ventrolateral prefrontal cortex	L	47	-42, -29, -14	5	5.15	< 0.001
	R	47	54, 35, 4	19	6.42	< 0.001
Amygdala	L		-30, -1, -26	33	6.28	< 0.001
	R		30, 2, -26	38	6.23	< 0.001

p-FWE = *p* value with family-wise error correction for the search volume.

BA, Brodmann area; FWE, family-wise error; H, hemisphere; K_e,cluster size; L, left; OCD, obsessive-compulsive disorder; R, right; *Z*, *Z* score.

[a] Significant at $p < 0.05$, whole-brain family-wise error corrected

Correlations with BOLD activation data

The present study identified that we found a negative correlation between the left VLPFC activation and the RT under the negative emotional distraction only in healthy controls (Spearman's $\rho = -0.579$, $p = 0.006$ in healthy controls; $\rho = 0.084$, $p = 0.724$ in OCD patients). Additionally, a positive correlation between the bilateral amygdala and distractibility rating scores on negative emotional pictures was found only in OCD patients (OCD patients, left: $r = 0.592$, $p = 0.006$; right: $r = 0.721$, $p < 0.0001$; healthy controls, left: $\rho = -0.052$, $p = 0.823$; right: $r = 0.056$, $p = 0.811$). The right amygdala in OCD patients also had positive correlations with the symptom provocation scores on negative emotional distracters ($\rho = 0.471$, $p = 0.036$).

DCM results

Model structure

In the initial model space, healthy controls displayed no significant unidirectional connection from the DLPFC to the amygdala; however, OCD patients showed all connections significantly. Therefore, an interconnected model with all three regions, which was found to be significant, was selected further DCM analyses (Figure 4).

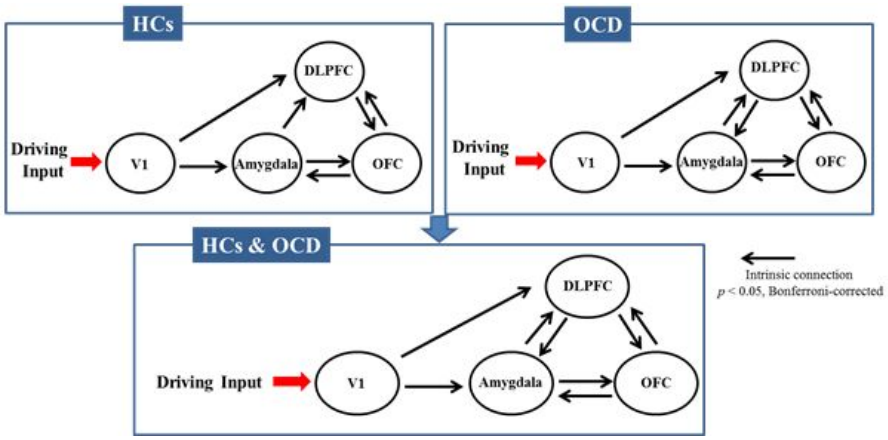

Figure 4. Bayesian model averaging yielded the intrinsic connectivity models in each group (first row). The connections significant in both healthy controls (HCs) and obsessive-compulsive disorder (OCD) patients were included further dynamic causal modeling (DCM) analysis (second row). Each arrow indicates intrinsic connectivity at $p < 0.05$, Bonferroni-corrected.

Intrinsic connectivity and modulatory effect by negative emotional distraction

Again, BMA was applied within each subject's 25 models and

one-sample and two-sample *t* tests were used for comparisons. The results of the intrinsic connectivity revealed no significant group differences (Table 5). As a result of the modulatory effect by negative emotional distraction, OCD patients showed a reduced modulation on the connection from the DLPFC to the OFC ($p < 0.05$, uncorrected). However, no significant modulatory effects were found on any connections in healthy controls. Comparison between groups showed that relative to healthy controls, OCD patients showed reduced modulation effects by negative emotional distraction on the DLPFC to the OFC connection, which was endogenously coupled in the positive direction ($p < 0.05$, Bonferroni-corrected; Figure 5 and Table 5).

Table 5. Baysian model averaging results

	OCD patients		Healthy controls		*Group comparisons* *p*-value
	Mean	S.D.	Mean	S.D.	
Modulation by negative emotional distraction					
Amygdala → DLPFC	0.00094	0.003	-0.00008	0.003	n.s.
Amygdala → OFC	0.00008	0.003	-0.00012	0.002	n.s.
DLPFC → Amygdala	0.00001	0.003	0.00081	0.003	n.s.
DLPFC → OFC	-0.00162*	0.002	0.00061	0.002	$p < 0.05$ corrected**
OFC → Amygdala	0.00081	0.004	0.00091	0.003	n.s.
OFC → DLPFC	0.00028	0.002	-0.00033	0.002	n.s.
Intrinsic connectivity					
V1 → Amygdala	-0.0066	0.052	0.0026	0.026	n.s.
V1 → DLPFC	0.0070*	0.041	0.0022	0.024	n.s.
Amygdala → DLPFC	0.0383**	0.085	0.0320*	0.061	n.s.
Amygdala → OFC	0.0056	0.019	0.0075*	0.026	n.s.
DLPFC → Amygdala	0.0171*	0.039	0.0184*	0.035	n.s.
DLPFC → OFC	0.0175*	0.079	0.0083*	0.041	n.s.
OFC → Amygdala	0.0054	0.031	0.0062**	0.008	n.s.
OFC → DLPFC	-0.0016*	0.046	0.0045	0.015	n.s.

Means and standard deviations (S.D.) of connectivity parameters for healthy controls and OCD patients (OCD). n.s., not significant; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex. **Bonferroni corrected; * $p < 0.05$, uncorrected.

Figure 5. Bayesian model averaging results. The values in the bar graph represent the means of modulatory effect parameter. The significantly reduced modulatory effects by negative emotional distraction on the connections from the DLPFC to the OFC were found only in OCD patients compared to healthy controls (*b*) ($p < 0.05$, Bonferroni corrected). V1 = primary visual cortex. ** Bonferroni corrected; * $p < 0.05$, uncorrected.

Discussion

This study demonstrates the disrupted neural interactions within brain circuits associated with emotion regulation in OCD patients. During the delay interval under negative emotional distraction, the OCD patients showed significant differences between groups in the DLPFC and OFC activations. However, both groups activated the amygdala the greatest. Additionally, modulation effects by negative emotional distraction on the connection from the DLPFC to the OFC, particularly in the anterior part, exhibited reduced connectivity levels in OCD patients, compared to healthy controls.

The present fMRI study reveals both healthy controls and OCD patients show similar patterns in the amygdala in response to general negative emotional stimuli, indicating strong disturbances by negative emotional pictures during the WM maintenance phase (Denkova *et al.*, 2010, Dolcos *et al.*, 2011, Dolcos and McCarthy, 2006). The increased amygdala under negative emotional distraction is consitent with a previous finding on higher level of fear of negative emotions in people with hightened obsessive-compulsvie symptoms (Stern *et al*., 2014). Interestingly, the bilateral amygdala was positively correlated with distractibility rating scores on negative emotional distraction only in OCD patients. Also, OCD patients had positive correlations between the right amygdala and symptom provocation rating scores on negative emotional distraction. The human amygdala has been considered a core

brain structure responsible for emotional processing, especially for aversive stimuli, and triggers the interference on cognitive tasks at hand (Dolcos *et al.*, 2011, Etkin *et al.*, 2006, Han *et al.*, 2013). Thus, the amygdala may be susceptible to subjective distractibility and symptom provocation in OCD patients.

OCD patients also exhibited between-group differences in the DLPFC and OFC during WM maintenance under negative emotional distraction, compared to healthy controls. The OFC has been considered to play a role in inhibitory cognitive processing and is associated with the DLPFC (Kwon *et al.*, 2009, Savage *et al.*, 1999). In previous studies, increased frontal and parietal activations including the DLPFC and presupplementary motor area were found in OCD patients during a cognitive task (Ciesielski *et al.*, 2005, Henseler *et al.*, 2008, de Wit *et al*., 2012, de Vries *et al*., 2014). Some of these studies found no group differences on behavioral task performances likewise our behavioral result (Ciesielski *et al.*, 2005, Henseler *et al.*, 2008, de Wit *et al*., 2012) and more interestingly, the other study found task-related hyperactivation in OCD patients with normal WM performance, in contrast to those with behavioral WM impairment (de Vries *et al*., 2014). All of these studies explain that hyperactivations in the cognitive task-related regions may relate to a compensatory neural recruitment (Ciesielski *et al.*, 2005, Henseler *et al.*, 2008, de Wit *et al*., 2012, de Vries *et al*., 2014). Therefore, it can be suggested that enhanced recruitments in the WM-related regions in OCD patients compensate for a detrimental effect of negative emotional distraction on WM

performance to reach a similar level of performance in healthy controls. Thus, the behavioral WM deficits may not be detected in OCD patients; however, the OCD patients may possess latent deficits (Henseler *et al.*, 2008, Pujol *et al.*, 1999).

Moreover, the results of the exaggerated recruitments in these prefrontal regions may support Freud's concept on the defense mechanism in terms of blocking or distracting confrontation of aversive stimuli through cognitive processing (Gabbard, 2010). Among the defense mechanisms, especially intellectualization could explain that the overactive top-down controls of the prefrontal regions may be used to help OCD patients block emotional stress by negative emotional distraction.

The novel aspect of the present findings was that the connection from the DLPFC to the OFC is negatively modulated by negative emotional distraction in OCD patients, compared to that in healthy controls. From this result, it can be inferred that the negative emotional distraction induced a dampening influence on the cortico-cortical interaction, which was not found in healthy controls. A convergence of OCD research has pointed to the dysfunction of cortico-striato-thalamo-cortical circuitry (Saxena *et al.*, 1998, Saxena and Rauch, 2000). However, a review of OCD pathophysiology points out that this circuitry is insufficient to explain the pathophysiology of OCD (Milad and Rauch, 2012). In fact, for instance, recent studies identified altered functional connectivity on the frontal-limbic circuitry in OCD patients (de Vries *et al*., 2014, de Wit *et al*., 2015, van Velzen *et al*.,

2015). Therefore, the present study validates this notion, and further reveals a dysfunction of cortico-cortical interaction in OCD patients. The OFC has been considered one of the key regions in the pathophysiology of OCD (Kwon *et al.*, 2009, Menzies *et al.*, 2008). The OFC promotes cognitive-affective interaction through its essential role to integrate and modulate neural activation (Rule *et al.*, 2002). It is also important to interact the DLPFC-OFC connection in cognitive functions, thus the OFC's disruption contributes to some mental disorders (Moghaddam and Homayoun, 2008). Therefore, our finding could be interpreted that general negative emotional distraction triggers exaggerated recruitment of the DLPFC in OCD patients when compared to healthy controls. This DLPFC hyperactivation may lead to reduce top-down input to the OFC and may further interrupt the integrations of cognitive control for inhibiting the detrimental effects of negative emotion.

This study had several limitations. First, medicated OCD patients were included in all analyses, so pharmacological factors cannot be excluded in this study. However, our findings were not significantly different from cognitive performance, BOLD-fMRI, or DCM analyses between medicated OCD and DNO/UMO patients. Second, OCD patients with other Axis I and II disorders were included; however, findings from both univariate and DCM analyses remain after excluding those 5 OCD patients.

In summary, the present study reveals altered effective connectivity from inputs in the DLPFC to the OFC under negative emotional

distraction in OCD patients, as well as abnormal activations in these brain regions. The exaggerated top-down signals in the DLPFC further reduce cortico-cortical interactions with the OFC, which may be responsible for dysfunctions of cognitive and emotional processing in OCD patients. The disrupted DLPFC-OFC connectivity under negative emotional distraction thus can be a neurobiological model in OCD.

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국문 초록

강박증 환자군의 부정 정서 하에 배외측 전전두엽에서 안와전두엽으로의 경로 이상

강박증은 인지 및 정서 기능의 이상과 연관이 있으며, 이러한 기능 장애는 정서를 조절하는 신경 회로 내의 상호작용 이상으로 여겨질 수 있다. 강박증 환자들의 인지와 정서 처리 기능 장애에 대한 기존의 많은 연구들이 있지만, 이러한 인지 및 정서의 상호작용 장애를 유발하는 신경 회로의 연결에 대해서는 밝혀진 바가 많이 없다. 따라서 본 연구에서는 동적 인과 모델링 (dynamic causal modeling)을 사용하여 강박증 환자들의 인지와 정서 처리 기능을 담당하는 신경 회로 내의 연결성에 대해 탐색하고자 하였다.

실험에 동의한 강박증 환자군 20명과 일반대조군 21명이 연구에 참여하였으며, 두 집단의 성별, 나이, 지능 및 교육연한은 통계적으로 유의한 차이를 보이지 않았다. 인지 및 정서 기능의 상호작용의 이상을 알아보기 위해, 3개의 서로 다른 얼굴 자극을 기억해야 하는 작업 기억 과제를 수행하는 동안에 부정 정서 및 중성적 사진을 방해 자극으로 제시하였다. 3.0T 자기공명영상장치를 이용하여 이러한 지연-반응 작업 기억 과제를 수행하면서 뇌 기능적 영상을 촬영하

였다.

본 연구의 관심 조건인 부정 정서가 주어진 상태에서 작업 기억 인지 기능을 수행하는 동안, 강박증 환자군과 일반대조군 모두 대표적으로 정서 처리 기능을 담당하는 편도체의 활성화가 관찰되었지만, 집단 간 유의미한 차이는 보이지 않았다. 하지만, 동일 조건 하에서 강박증 환자군은 일반 대조군과는 대조적으로 배외측 전전두엽 영역의 과활성화를 보여주었다. 또한, 안와 전두엽 영역에서도 동일 조건 하에서 유의미한 집단 간 차이를 보였다. 동적 인과 모델링을 동일 조건에 적용한 결과, 강박증 환자군은 일반대조군에 비해 부정 정서 하에서의 작업 기억 인지 기능 처리를 할 때 배외측 전전두엽에서 안와 전두엽으로 가는 경로의 연결성이 유의미하게 감소하는 것이 관찰되었다.

결론적으로, 강박증 환자군은 부정 정서가 방해 자극으로 주어진 상황에서 작업 기억 인지 기능을 처리하기 위해 배외측 전전두엽 영역의 과도한 활성화를 보였으며, 이러한 과활성화는 더 나아가 안와 전두엽으로 가는 경로의 연결성에 이상을 초래하였다. 따라서 본 논문은 강박증 환자의 인지 및 정서 기능의 상호작용 이상을 확인하였을 뿐 아니라, 이러한 기능의 장애는 배외즉 전전두엽 영역에서 안와전두엽으로 가는 연결성 감소와 연관이 있음을 보여주었다. 이러한 대뇌피질 간 연결성의 이상은 강박증을 이해하기 위한 새로운 모델을 제시할 수 있을 것으로 보인다.

주요어: 배외측 전전두엽, 정서, 뇌기능자기공명영상, 강박증, 안와전두엽

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